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| 10/080,713 | 02/25/2002 | Alan Colman | 1966.0020003/BJD/FRC | 9155 |

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| EXAMINER | |
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| TON, THAIAN N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/080,713 | COLMAN ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *62-66, 70-73, 75-90, 98-100, 102-127, 131-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-66,70-73,75-90,98-100,102-127 and 131-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' Amendment and Response, filed 4/27/06, has been entered. Claims 62, 63, 90, 131-133 are amended; claim 67 is cancelled; claims 62-66, 70-73, 75-90, 98-100, 102-127, 131-133 are pending and under current examination.

The Piedrahita Declaration, filed 5/11/06, has been considered.

### *Information Disclosure Statement*

Applicants' Supplemental IDS, filed 4/27/06, has been considered and made of record.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-66, 70-73, 75-90, 98-100, 102-127, 131-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record, advanced in the prior office action, mailed 10/21/05.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Oback *et al.* Applicants' argue that it was not considered unpredictable which mammalian somatic cells could be used to donate genetic material, as any somatic cell could be used. Applicants point to the Ayares and Piedrahita Declaration as evidence of this. Applicants argue that cloning efficiency is different than clonability, and there is no requirement, under U.S. Patent laws that require that a technique be highly efficient, or work perfectly to be part of the patentable process. Applicants argue that Table 1 of the of Oback *et al.*, which delineates various cloning efficiencies and was referred to in the prior Office action, is addressed by the Ayares Declaration, which established that there is no fundamental reason why any somatic cell, with a normal karyotype, cannot act as a nuclear donor, and that the issue of cloning efficiency is simply one of numbers – some somatic cells are more efficient than others, for reasons described by the literature at the time, and discussed by the Examiner previously. Applicants argue that the response to low efficiency donor cell is simply to conduct more of the same embryo transfers, until viability is achieved, and that the Ayares Declaration states that repeating the experiment enough times to achieve success does not require a special, or extra technique, it simply requires that one carry out the experiment more times, and that the fact that repetitive laboratory work is not required is not in itself indicia of undue experimentation. See page 11 of the Response.

Piedrahita Declaration. Applicants provide this Declaration as support for their arguments and Ayares Declaration. The Declaration states that it was understood and well-accepted that the genetic material from any somatic cell could be used in somatic cell NT, and that it was understood that the more differentiated the cell, the less efficient the reprogramming might be, however, this was expected and accounted for, because the first cloned animal was produced using an adult, fully differentiated somatic cell as a nuclear donor (Dolly). See page 12 of the Response. Furthermore, Applicants' response states that low cloning efficiency simply meant that more transfers were required to achieve success, and that, at the

time of filing, Dr. Piedrahita knew of no somatic cell that, for theoretical or technical reasons, could not be used as a supply of genetic material for cloning, or in particular, mammalian cloning. See also, #14-16 of the Declaration. The Declaration states that fetal fibroblasts are typically used for SCNT, but other somatic cell types, including follicular cells, can be used to produce live offspring (#17 of the Declaration); and if a cell, other than a fetal fibroblast, were to be used in order to achieve a clone, there would be transfer of up to 2000 embryos, and that this would be considered routine lab work. Furthermore, if an efficient or difficult cell line were used as nuclear donor, more time and resources would be committed, but could be carried out using standard techniques. See #18 of the Declaration. Dr. Piedrahita agrees with the Ayares Declaration, in that the concept tf cloning efficiency is simply a reflection of the ratio number of attempts and not an indication of lack of clonability of the cell (#19 of the Declaration). The declarant comments on the Oback *et al.* paper, stating that the low cloning efficiencies of the somatic cells listed in Table 1 describe populations of cell experiments that are too small to reach any definitive conclusion on an accurate cloning efficiency. The Declaration further states that there is no good scientific rationale to support the position that any given somatic cell cannot be cloned (#20). See also, pages 13-14 of the Response.

Response to Declaration and Arguments. These arguments and the Piedrahita Declaration are fully considered, but not persuasive. Under 112, 1st paragraph, for enablement, the test of enablement is not whether any experimentation is necessary, but if it is undue. Although there is no requirement that a technique be highly efficient, or work perfectly, the experimentation that would be required to implement the invention must not be undue.

MPEP §2164.03 states that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. ... The more that is known in the

prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling." Further, "The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, there is a lack of predictability in the art. Accordingly, what is known in the art provides evidence to the question of predictability."

Applicants' are not arguing the invention as a whole, which is what enablement entails; instead, Applicants are arguing with regard to each method step. The claimed method as a whole must be enabled. It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513. Nuclear transfer, as a method, may be well known, but determination of the state of the art at the time of filing, and consideration of the working examples in the specification, provide sufficient evidence that this

technology is unpredictable with regard to what cell types to use as donors, particular oocytes (for example MII or telophase II), and the subsequent activation, and further development of the NT unit to form a live born offspring. Thus, although one could conduct more embryo transfer, this is only one step of the claimed invention, the full scope of the claims require successful transfection of the somatic cell (which includes cell lines and primary cells, for example), the selection of the transfected somatic cell, the development of the resultant NT unit to form a live born animal, and these steps as a whole (which constitute the claimed invention) are not found to be enabling, for reasons set forth previously (see also Fulka, Oback, Campbell, Tian and McEvoy, cited previously). Finally, it is noted that Applicants' arguments and the Piedrahita Declaration are directed to using untransfected somatic cell types for NT. The claims require transfection of a somatic cell, to be used in NT. Specific targeting of an endogenous locus in a somatic cell is not found to be unpredictable, as shown in the prior Office actions.

Campbell/Tian/Li. Applicants argue that Campbell, like Ayares and Piedrahita, acknowledge that SCNT work across a "plethora" of donor cell types. Applicants argue that there is no statement in the Campbell article that any given somatic cell cannot be used for NT, nor that success cannot be accomplished. Applicants argue that there is no requirement under U.S. Patent law that one claim or use only a "most appropriate" embodiment, and that because many cell types have been shown to work in NT methodologies, the claims are enabled (see pages 14-15). Applicants argue that Tian state that there is no clear consensus on a superior somatic cell type to be used in NT, and that Applicants are not required to claim a "superior" embodiment. Applicants further argue that Li *et al.*'s teachings that NT is inefficient, does not render the claimed invention non-enabled, and simply because most of the cloned animals fail to develop to term and show some abnormalities, people working in the field of SCNT live with low efficiency results and expect them when performing NT and cloning. See page 16 of the Response.

Applicants argue that McEvoy only shows that the NT methodology is inefficient, and not that it does not work, and that McEvoy are merely focused on improving the efficiency of NT. See page 16 of the response.

These arguments are considered, but not persuasive. The Examiner is not arguing that one could not 1) use any untransfected somatic cell type for NT, and similarly 2) that homologous recombination does not occur in all cell types. Rather, the Examiner has determined, given Applicants' working examples as well as the state of the art at the time of filing, that it would be unpredictable to specifically targeting of an endogenous locus of a somatic cell, and then use the resultant, transfected cell in methods of NT to produce a live born animal. This is the invention as a whole. Because different cell types have different developmental capabilities, as well as the unpredictability with regard to homologous recombination in any cell type (as broadly claimed), it would not be predictable to use any cell type, modify its genome at a specific locus, and then use this cell to produce a live born mammal, as instantly claimed. Although there is no requirement for a "most appropriate" or "superior" embodiment, the breadth of the claims must be enabled. This is not the instant case, as stated previously. One of skill in the art would recognize that NT, in itself is inefficient in producing live born animals (as evidenced by Applicants' Declaration). Coupled with the inefficiency of producing live born animals, using any cell type, the claims require the specific targeting of an endogenous locus in the somatic cell. One of skill in the art would recognize that homologous recombination, at a specified target, is also inefficient and unpredictable.

Wands. Applicants argue that the present fact pattern is strongly analogous to the fact pattern in Wands, in which the CAFC overturned a PTO decision of nonenablement. Applicants argue that in the present case (i) both the specification and published literature as of the priority date taught how to routinely carry out the somatic cell NT process, (ii) the Piedrahita Declaration states that researchers

at the time of filing were highly skilled and educated, and were considered the "elite" of the animal veterinary research profession; (iii) all of the methods needed to practice the claimed invention were well known and (iv) the nature of NT technology is that it involves the routine preparation and implantation of cloned embryos to determine which ones will mature to viability. Applicants argue that the test for undue experimentation is not the amount, but if it is merely routine, or if the specification provides enough guidance to enable the determination of how to practice the claimed invention. Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.

These arguments are considered but not found to be persuasive. Applicant correctly asserts that a large amount of experimentation is acceptable if that experimentation is merely routine. However, the amount of experimentation required to make and use the full scope of the claimed invention, as evidenced by the prior Office actions, is more than simply routine. Applicants have provided Declarations stating that using FACS- and PCR-based technologies are routine to screen for homologous recombination events. Applicants have provided Declarations stating that cloning animals using any untransfected somatic cell is routine. There is no evidence of record, that the invention as a whole is routine. As stated here and in previous Office actions, one of skill in the art would need to practice undue experimentation to target an endogenous locus in a somatic cell, grow and select the cell, and then use this cell as a nuclear donor to produce a live born non-human mammal. The claims are directed to producing <u>any</u> transgenic non-human animals, using nuclear transfer, which is far from routine. Applicant suggests that developing transgenic animals is analogous to screening for antibody producing hybridomas and suggests that the finding in *In re Wands* supports enablement for their broad claims. However, it should be noted that the claims in *Wands* were limited to a single class of antibody capable of detecting a single antigen, as opposed to the broad scope of producing transgenic non-human animals

comprising any modified, endogenous gene locus by nuclear transfer. The Court in *Wands* reasoned as follows (1406-1407; emphasis added):

> When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

In contrast to the facts in *Wands*, the instant claims are tremendously broad, the production of transgenic animals by nuclear transfer is not routine and the instant application only provides working examples utilizing specific donor cells, specific recipient cells, to produce specific animals.

Homologous Recombination. Applicants' argue that the Ayares Declaration confirmed that it was feasible, as of the priority date, to obtain and screen for homologous recombination in cell types that do not have high proliferative potential, using the PCR techniques published in Zimmer & Gruss. Applicants argue that the techniques applied by Zimmer and Gruss are not just applicable to ES cells, but are non-cell dependent. Applicants argue that as early as 1989, various methods, including PCR-based methods and FACS-based methods, were known to those skilled in the art and could be used to detect targeting events after homologous recombination, within 3-5 days. Applicants argue that FACS has been used to detect events in transfected cells in all cell types, and that the Jasin paper (cited previously) was a fundamental publication that established the importance of this strategy for gene targeting, particularly with regard to a 700-fold enrichment for homologous versus nonhomologous integration events by using FACS to select targeted cells (p. 20 of the Response). Applicants argue that the Piedrahita Declaration confirms that cells need not be highly proliferative, or even moderately proliferative, to undergo targeting by homologous recombination. Rather, the technique only requires that the cell recombines. Furthermore, Dr. Piedrahita agrees with Dr. Ayares that it was well described in 1999 to obtain and screen for homologous recombination events using PCR and FAC-based screening regardless of whether the genetically modified cells had high proliferative potential, and that these methods permitted a research to detect targeted integration events without prolonged *in vitro* growth and expansion, and that the methods are independent of what kind of cell is transfected. Furthermore, Applicants argue that it is irrelevant that the Zimmer & Gruss paper focuses on ES cells, or that the Jasin paper focuses on cultured cells, because the techniques are equally applicable to all cell types. See pages 20-21 of the Response.

These arguments are considered, but not found to be persuasive. In Applicants' response, filed 7/16/04, Applicants state, on the record that, "One of

ordinary skill therefore would have had no reasons to predict that the nuclear genome of a somatic cell could be modified at an endogenous locus by a genetic targeting event and that the nucleus of the genetically modified somatic cell could be used to accomplish successful NT, prior to the work of the present inventors. Thus, it is clear that the present invention provides results that were not expected in view of knowledge available in the art as of the filing date of the present application." See page 23 of the Response, filed 7/16/04. This response further states that it is unexpected result that a primary somatic cell can be modified by *in vitro* gene targeting and can subsequently support successful NT to produce a healthy animal. See page 22 last ¶ of the Response filed 7/16/04. Thus, there is a contradiction between Applicants' statement and the Declarations as presented, that homologous recombination and gene targeting of somatic cells would be considered routine and not require undue experimentation.

The Piedrahita Declaration states that the FACS and PCR techniques to any cell type. The prior rejection is not stating that one could not use PCR or FACS-based techniques to detect homologous recombination events, it is directed the specific targeting or a specific endogenous locus in the genome of a somatic cell, the selection of an cell that has been targeted, and use of this cell in NT methods. One of skill in the art would need to practice undue experimentation to specifically target a particular gene, in the genome of a somatic cell, and modify this particular gene, and then identify and select recombinant cells. The working examples in the specification are directed to specific cell types (fetal fibroblasts, and primary mammary epithelial cells). However, as stated in prior Office actions, Thomson shows that premature senescence often occurs in gene targeted cells, which makes it difficult to confirm a targeting event in somatic cells, and this is supported further by Polejaeva & Campbell.

With regard to the Zimmer & Guss reference, directed to homologous recombination in an ES cell, art at the time of Applicants' priority date states that,

"The reasons that gene targeting has been so difficult in somatic cells is that the absolute frequency of homologous recombination in somatic cells is some two orders of magnitude lower that in ES cells. To complicate matters further, frequencies of nonhomologous recombination are typically very high." See page 88 of Sedivy *et al.* (**TIBS**, 15(3): 88-90, March 1999, cited on Applicants' IDS, filed 5/22/02, Document #AS26). Sedivy *et al.* review the state of the art of somatic cell gene targeting, suggesting various methods to improve recombination and targeting efficiency. Thus, one of skill in the art, at the time of filing, although recognizing that homologous recombination was present in somatic cells, would also recognize that it would be unpredictable to specifically target a particular locus, in any somatic cell (as instantly claimed), by any method (as broadly encompassed by the claims) in order to produce a gene-targeted somatic cell that could then be used in NT methodologies. Although the art cited by Applicants postulate that the methods used could be used theoretically on any somatic cell type, there is no enabling disclosure that any somatic cell type (for the breadth claimed) would work in the claimed methods. For example, no guidance is given in the specification, or cited art of record, with regard to targeting cells that do not divide (such as neurons), and then use of these cells in NT methods to produce a live born, transgenic animal. Accordingly, it is maintained that the claims are not enabling for the breadth, as instantly claimed.

Recipient Cells. Applicants have now amended the claims to recite that the donor cell is "capable of producing a viable nuclear transfer unit" (see claim 62, part (b), for example). Applicants argue that this address the Examiner's concerns about the cell cycle of the recipient, and that they have not amended the claims to specify that the recipient cell need to be enucleate, because it does not be enucleate, rather, the reconstructed embryo can be enucleated to restore the proper chromosomal complement, known to those skilled in the art. See page 21, part (iii) of the Response.

These arguments are considered, but not persuasive. The specification does not provide sufficient guidance to any other cells, other than enucleated oocytes, two-cell embryos or zygotes that can be used as recipient cells in NT. Although the reconstructed embryo could be enucleated to restore the proper chromosomal complement, these steps are not supported by the instant claims. The claims require development of a live born mammal. Applicants have not pointed to support with regard to enucleation of the reconstructed embryo, and this step is not present in the amended claims, and thus, is beyond the scope of the instant rejection. Because removal of the genome of the cytoplast recipient is a critical and necessary step, in order to produce a mammal, it is required to enable the claims.

Species/Genus. Applicants have now amended the claims to recite transferring the NT unit to a surrogate mother which is a suitable host. The specification does not provide specific guidance for a suitable host surrogate mother, for the breadth claimed. Although the specification teaches that a sheep can be a suitable recipient for bovine, ovine and porcine (p. 19, lines 1-9), the claims are broadly directed to production of any non-human mammal. The specification fails to provide specific guidance, for the breadth of the claims, with regard to a suitable recipient mother. Accordingly, it is reiterated that Applicants amend the claims to clarify that the NT unit, embryo and surrogate mother are of the same species, in order to enable the claim.

Abundant Expression. Applicants' cancellation of claim 67 overcomes the prior rejection with regard to abundant expression.

Genotype/Phenotype. Applicants argue that while the transgenic animals may not at all times display genetic changes, these animals are genotypically altered and are thus statutory subject matter as material altered by man, and have an important use in breeding. See page 22 part (vi) of the Response.

These arguments are not persuasive. Firstly, the prior rejection does not claim that the animals are not "statutory subject matter", as this would be a

rejection under §101, which is not the case. Specific embodiments of the claims are directed to targeting using a specific promoter, see claims 70-73, 102-105, for example. The claimed embodiments are directed to placing a promoter adjacent to an endogenous gene in the nuclear genome, wherein the promoter is the collagen gene promoter, or a milk protein gene promoter. Although one of skill in the art may be able to identify a transgenic animal, one could not predict what phenotype this animal would exhibit. Thus, without a particular phenotype, there is no enabled use of the particular animal. Applicants have not provided specific guidance with regard to the embodiments that encompass these specific genetic modifications, and one of skill would not be able to rely upon the art to predict the phenotype of the resultant animal. The instant claims are not enabling because they claim transgenic animals which do not have an apparent phenotype, and thus, one of skill would not know how to use these animals. Thus, it is maintained that the specification fails to provide specific guidance for the breadth of producing any transgenic non-human animal whose genome comprises a modification at an endogenous locus by a gene targeting event, and thus, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing a particular transgene, the levels of the transgene product, the consequences of that product, and the resulting phenotype.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods, with a predictable degree of success, to implement the invention as claimed.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***tnt***
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